UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/769,204	01/24/2001	Malcolm R. Alison	54113-8004.US01	4799

7590 06/02/2003

Perkins Coie LLP
Patent- LA
P O Box 1208
Seattle, WA 98111-1208

EXAMINER	
SULLIVAN, DANIEL M	
ART UNIT	**PAPER NUMBER**
1636	17

DATE MAILED: 06/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Application No.	Applicant(s)
09/769,204	ALISON ET AL.
Examiner	**Art Unit**
Daniel M Sullivan	1636

Office Action Summary

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26,27 and 51-65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26,27 and 51-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This Office Action is a response to the Request for Continued Examination and "Amendment and Response" (Paper No. 16) filed in reply to the Final Office Action mailed 11 February 2003 (Paper No. 13). Claims 26-51 were considered in Paper No. 13. Claims 28-50 were canceled and claims 52-65 were added in Paper No. 16. Claims 26, 27 and 51-65 are pending and under consideration herein.

Claim Objections

Claim 51 is objected to because of the following informalities: The claim uses the abbreviation HGF without definition. The meaning of each abbreviation should be set forth the first time the abbreviation appears in the claims. Appropriate correction is required.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 26 and 27 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 11 of U.S. Patent No. 6,248,725 (hereinafter '725). Although the conflicting claims are not identical, they are not patentably distinct. The instant claim 26 is directed to a method for improving the efficiency of *in vivo* liver cell retroviral transduction comprising concurrently administering T3 and KGF and further comprising a retroviral vector complexed with cationic liposomes subsequent to the induction of liver cell proliferation. Claim 27 limits the cationic liposomes to comprising DOGS. Claim 11 of '725 is directed to a method comprising each of the method steps and limitations of the instant claims 26 and 27 except for complexing the retroviral vector with cationic liposomes comprising DOGS. In the paragraph bridging columns 6 and 7, '725 teaches that the most preferred vector composition is a retrovirus complexed with cationic liposomes, in particular DOGS. Thus, the limitations of the instant claims 26 and 27 would have been obvious to one of ordinary skill in the art in possession of claim 11 and the cited teachings from U.S. Patent No. '725.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 51-65 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating cirrhosis of the liver, does not reasonably provide enablement for a method of preventing cirrhosis of the liver. The specification does not enable

any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Although the subject matter of claim 51 was previously indicated as allowable, upon further consideration of the art and arguments of record, the teachings of the specification and prior art would not enable the skilled artisan to prevent cirrhosis without engaging in undue experimentation.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention and Breadth of the claims: The claims encompass a method of preventing cirrhosis of the liver comprising concurrently administering to a subject an effective amount of T3 and an effective amount of KGF, and further comprising administering to a liver cell a retroviral vector complexed with cationic liposomes wherein the retroviral vector encodes HGF. As the specification does not define the term "preventing" the claim is interpreted according to the standard dictionary definition of the term "prevent", i.e., "to keep from happening or existing" (Merriam-Webster Dictionary). Thus, the claims encompass a method of

precluding the existence of cirrhosis of the liver, regardless of the circumstances that might give rise to the cirrhosis.

State of the prior art and Level of predictability in the art: The relevant art, exemplified by Scheur, P.J. (Section 7.1: cirrhosis and chronic active hepatitis *in* Oxford Textbook of Clinical Hepatology, Volume 1, (McIntyre *et al.*, eds.) Oxford University Press, 1991), Rojkind *et al.* (Section 7.2: Pathophysiology of liver fibrosis, *in* Oxford Textbook of Clinical Hepatology *Id.*) and Erlinger *et al.* (Section 7.3: Cirrhosis: clinical aspects, *in* Oxford Textbook of Clinical Hepatology, *Id.*), teaches that cirrhosis of the liver has several distinct etiological agents and pathogenetic pathways. These include virus-, autoimmune-, and drug-induced necrosis and inflammation of various types; alcohol-, diabetes-, and obesity-induced steatosis; and fibrosis and cirrhosis arising from chronic biliary obstruction or venous outflow blockade (see especially "Aetiological agents and pathogenetic pathways" beginning in the first column on pate 371; see also Table 1 of Erlinger *et al.* at page 380). Thus, cirrhosis can develop as the product of an infectious and/or inflammatory process, acute or chronic toxicity, metabolic disease, obstruction of bile ducts or veins, etc. Furthermore, there appears to be distinct pathways leading to cirrhosis. In the conclusory statements on page 379, Rojkind *et al.* characterizes the system of liver cirrhosis as very complex and speaks of a network of cytokines and growth factors important in modifying cell proliferation and production of extracellular matrix during the development of liver cirrhosis. In the second column on page 387, Erlinger *et al.* teaches that prognosis of cirrhosis depends on etiology, epidemiologic setting and clinical and laboratory manifestations. Thus, the art teaches that the development of liver cirrhosis is a complex process having divergent etiologies and pathogenetic pathways. A search of the recent art provides no teachings

that would indicate that merely stimulating hepatocellular proliferation and administering a vector encoding HGF would effectively prevent the development of cirrhosis having any given etiology, let alone all possible etiologies, particularly in view of the fact that liver cell proliferation is already a feature of the cirrhotic liver (see especially Erlinger *et al.*, the section entitled "Definition" on page 380). Given the unpredictability of preventing liver cirrhosis using the instant claimed method and the lack of teachings from the art regarding how liver cirrhosis of diverse etiology can be prevented by inducing liver cell proliferation, the skilled artisan must turn to the teachings of the specification for guidance in such clear, concise and complete terms as to enable practicing the method for the stated purpose of preventing liver cirrhosis.

Amount of direction provided by the inventor and existence of working examples: The specification discloses methods of increasing transduction efficiency of hepatocytes comprising inducing a semi-synchronous wave of *in vivo* liver cell proliferation, and provides actual reduction to practice of the method in normal rats. With regard to preventing cirrhosis, the specification provides no evidence that the disclosed method would be capable of halting the progression of liver diseases resulting from hepatitis, biliary obstruction, toxins, metabolic diseases, etc. such that cirrhosis would not develop. Given the progressive nature of these conditions, it would seem unlikely that the disclosed method could effectively prevent the development of cirrhosis in the face of continuing liver damage from the underlying disease. The specification is silent with regard to what additional steps might be taken such that the disclosed method can be used to prevent development of cirrhosis regardless of the etiology of the cirrhosis.

In response to rejection of the claims in a previous Office Action under 35 U.S.C. §112, first paragraph, as lacking enablement, Applicant argues that the claims are enabled for treatment because, "the method of treatment claims are just that: a method of treatment, and not necessarily a cure" (Paper No. 8, filed 5 July 2002, paragraph bridging pages 13 and 14). In contrast, a method of preventing cirrhosis is essentially a method of curing. That is, Applicant is claiming a method which is capable of halting the complex processes leading to cirrhosis such that a liver that would have become cirrhotic in the absence of the method does not develop cirrhosis.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: The relative level of skill in the art is high. However, for the reasons set forth above, the skilled artisan would not expect to be able to prevent the development of cirrhosis using the instant claimed method without additionally removing the underlying cause of the liver disease. There is nothing in the art to suggest that merely increasing liver cell proliferation according to the disclosed method would prevent the development of cirrhosis resulting from any conditions. As the claims encompass a method of preventing liver cirrhosis regardless of the etiology of the disease, the skilled artisan must extend the teachings of the specification, which are limited to a method of increasing the efficiency of transfection of liver cells *in vivo* and a recitation of HGF as one of many possible proteins that could be expressed in the liver, such that development of cirrhosis can be prevented regardless of whether the disease is a result of viral infection, alcoholism or other drug abuse, biliary obstruction, porphyria, albetalipoproteinaemia, glycogen storage diseases, Wilson's disease, sarcoidosis, syphilis, or veno-occlusive disease among others. As each of these diseases is likely to have its own set of obstacles to effectively preventing the development of cirrhosis, the skilled artisan is left to address each of these

obstacles without any guidance from the Inventor as to how to proceed. Thus, the skilled artisan could not practice the claimed invention commensurate with the scope of the claims without first engaging in blind trial and error experimentation to identify the method steps that must be added to those set forth in the claims so that the method can be used according to its stated purpose. Clearly, this would require that the skilled artisan seeking to practice the claimed subject matter engage in undue experimentation.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-746-9105 for regular communications and 703-746-9105 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

dms
May 29, 2003

JAMES KETTER
PRIMARY EXAMINER